Armed Forces College of Medicine

AFCM

Autoimmunity

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INTENDED LEARNING OBJECTIVES (ILO)

- **By the end of this session the student will be able to:**

1. **Define immunologic tolerance**
2. **Discuss mechanisms of central & peripheral tolerance**
3. **Outline causes of autoimmune diseases**
4. **Classify autoimmune diseases**
5. **Explain mechanisms involved in tissue injury**
6. **Define most important examples of autoimmune diseases**
7. **Explain different treatment strategies of autoimmune diseases**

Definition

- **Autoimmune disease:**

Adaptive IR attacking own body tissues

Occurs due to failure of tolerance

Self Tolerance

* **Self Tolerance:**

It is a specific immunologic unresponsiveness to self antigens

i.e. the absence of specific immunoresponses to a particular antigen in a fully immunocomptent person

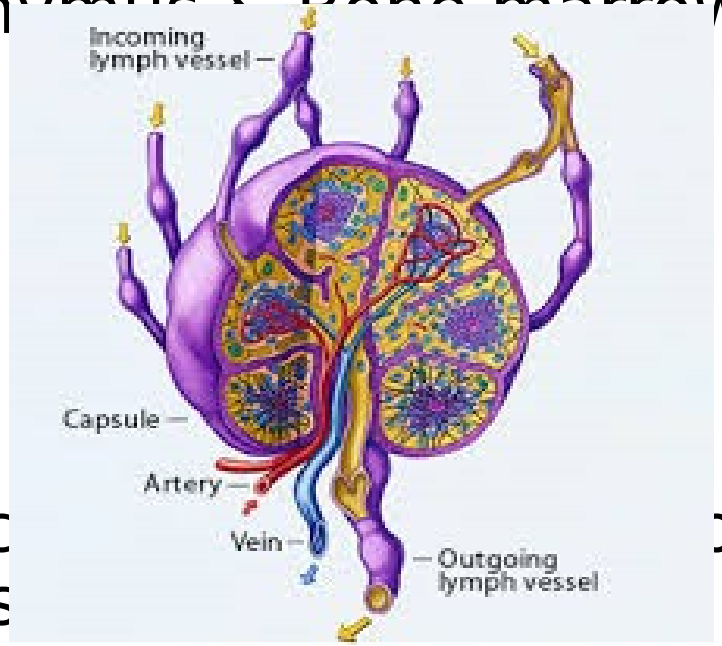
*** Both B-cells and T-cells participate in tolerence**

*** T-cells play the primary role**

Types of tolerance

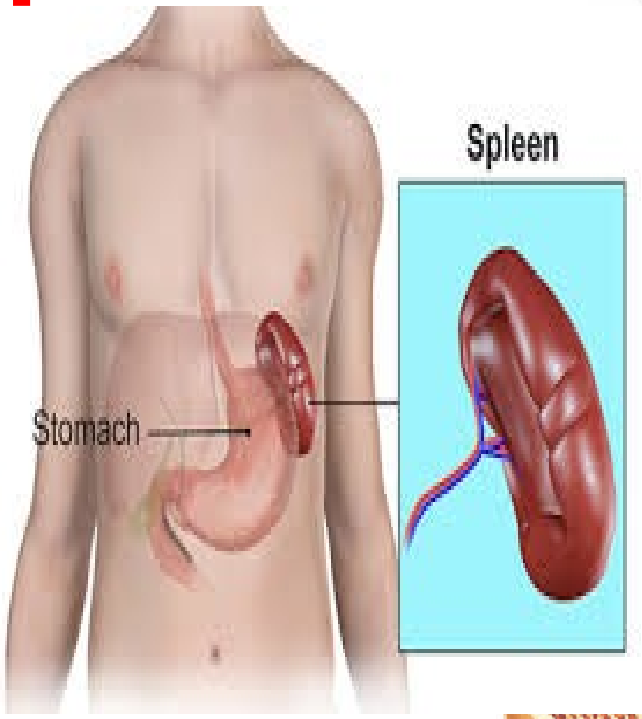
I-Central tolerance:

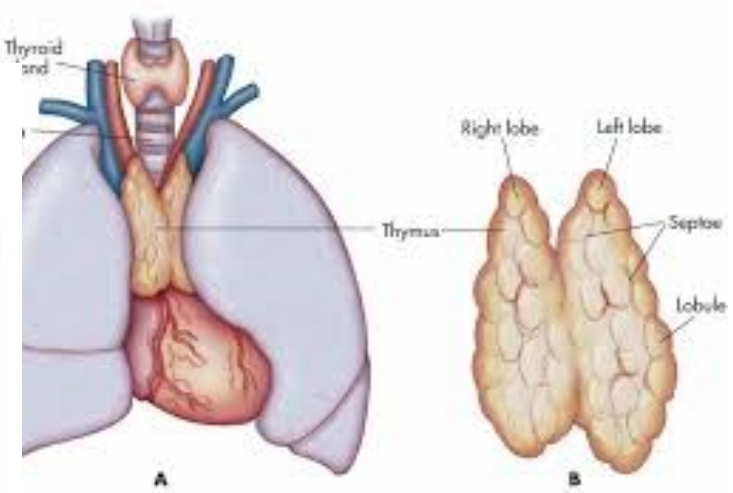
Occurs in 1ry lymphoid organs
Thymus & Bone marrow.

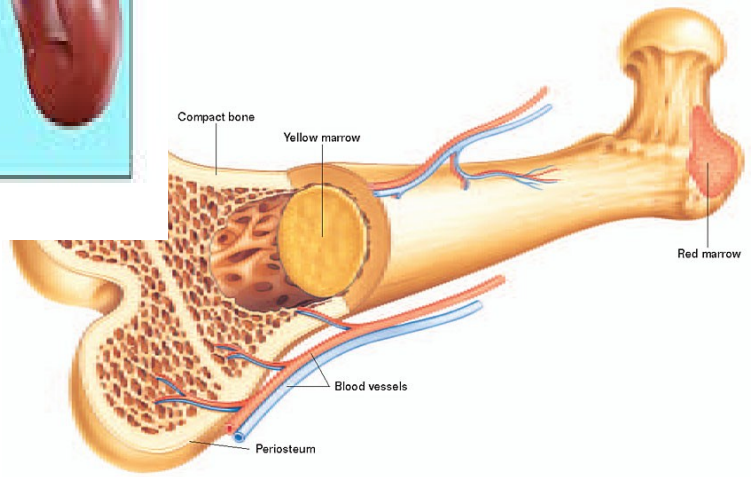


II-

Occ organs
&s







I- Central Tolerance

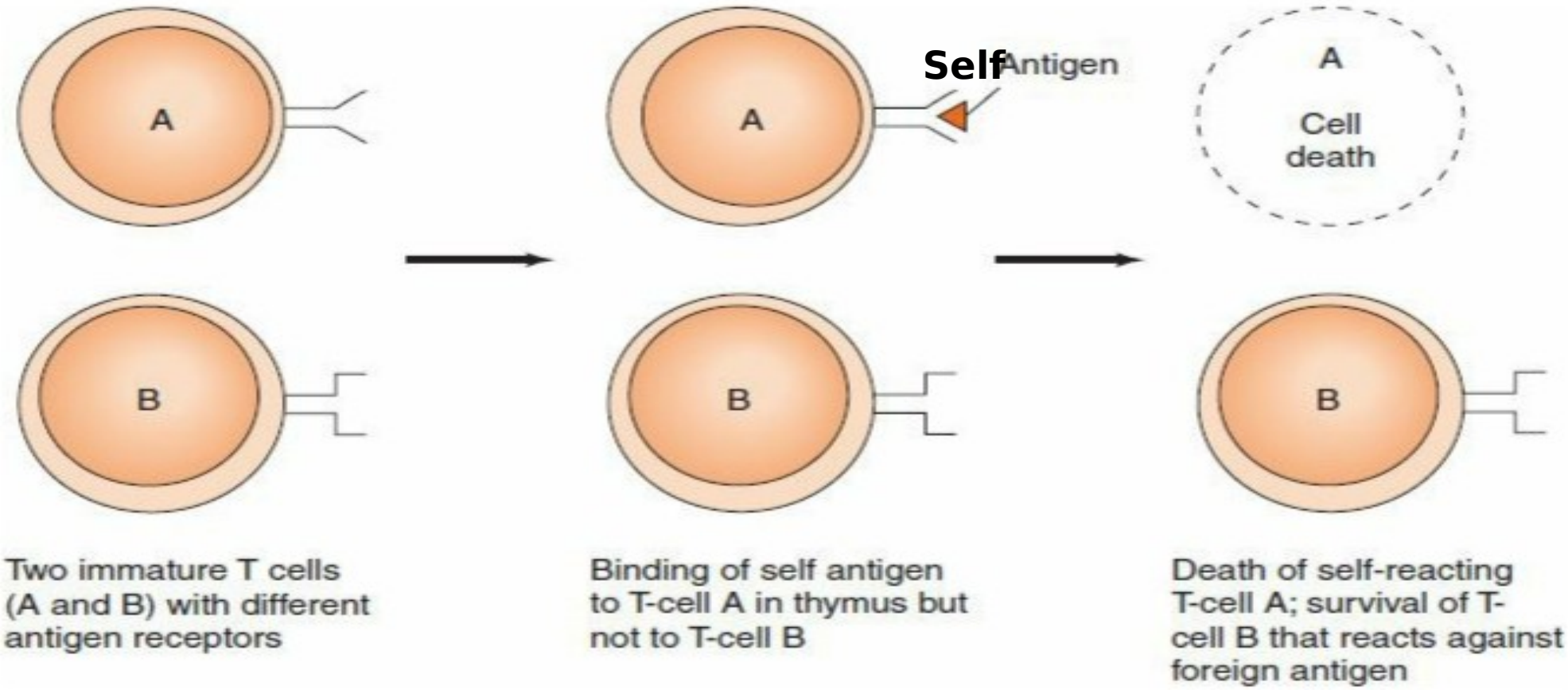
A- Death (Clonal-deletion / negative selection)

Occurs mainly during fetal life

* **The process by which T-cells acquire the ability to distinguish self from non self, in fetal thymus**

* **This involves the killing(inducing apoptosis) of immature T- cells that react against self antigens .**

Tolerance


A
B
A
Self Antigen
B
A
Cell death
B
Two immature T cells (A and B) with different antigen receptors
Binding of self antigen to T-cell A in thymus but not to T-cell B
Death of self-reacting T-cell A; survival of T-cell B that reacts against foreign antigen

I- Central Tolerance

B- Receptor editing (B lymphocytes only)

- **Immature B cells that produce a receptor for antigen (BCR) that would bind self-components undergo a process of receptor editing.**

- **If they fail to form a new BCR that is not a threat, they commit suicide (apoptosis).**

II- Peripheral Tolerance

Occurs postnatally

- ***by inhibition or deletion o***
  Self Reactive mature *T ce*

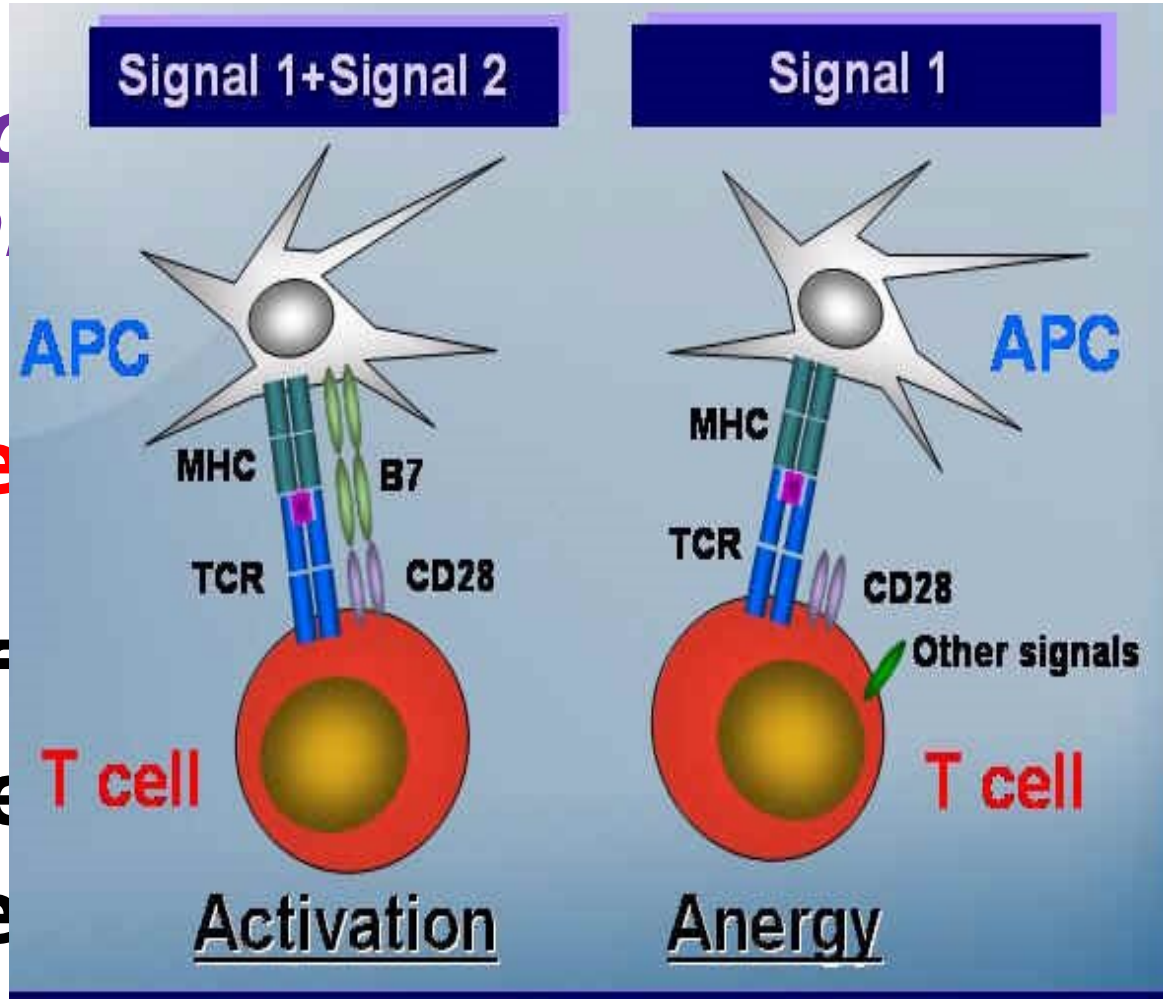
i.e escaping – ve selection

A. Clonal anergy (absence
costimulation signal):

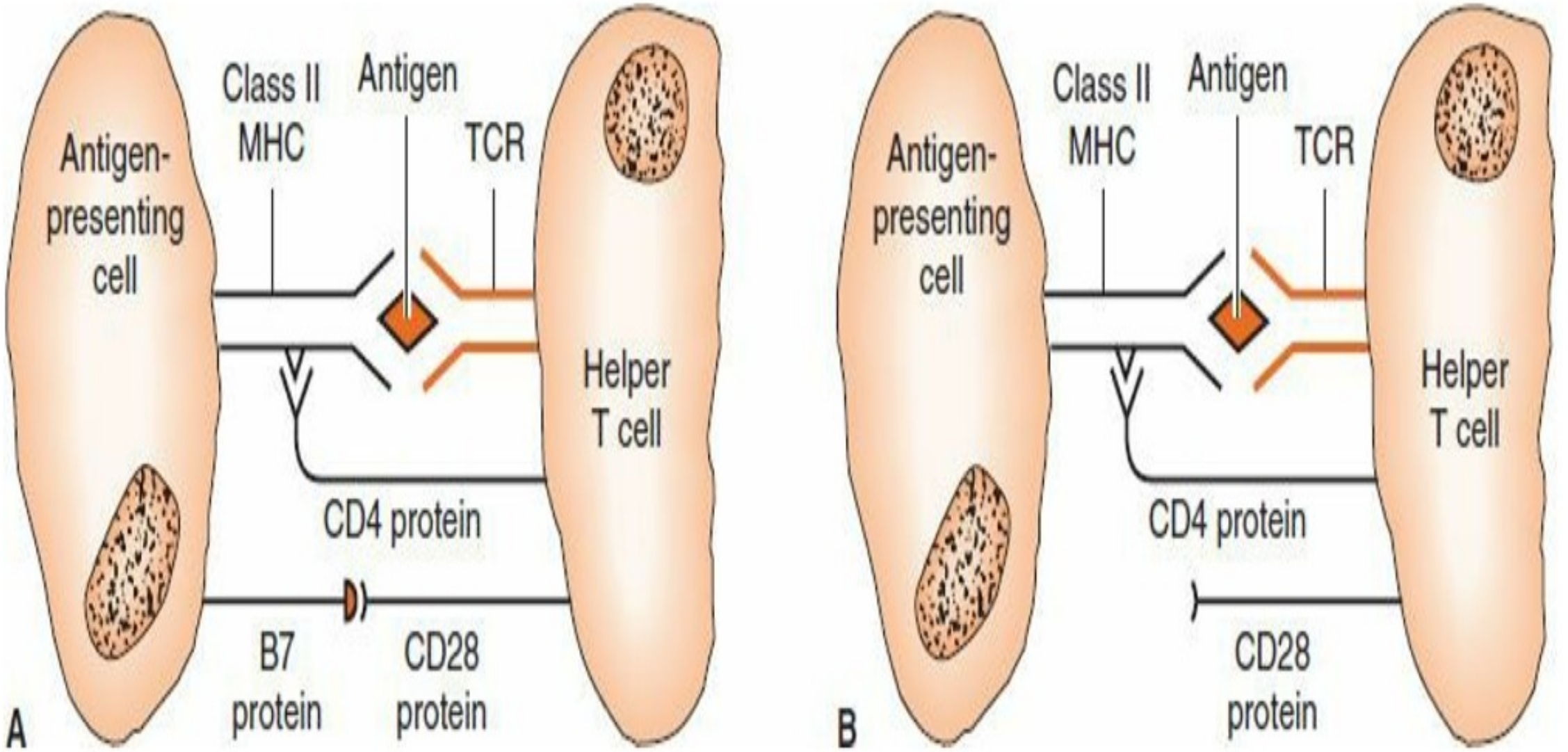
- **Functional inactivation of**

surviving self-reactive T ce

- **It is a growth arrest state**

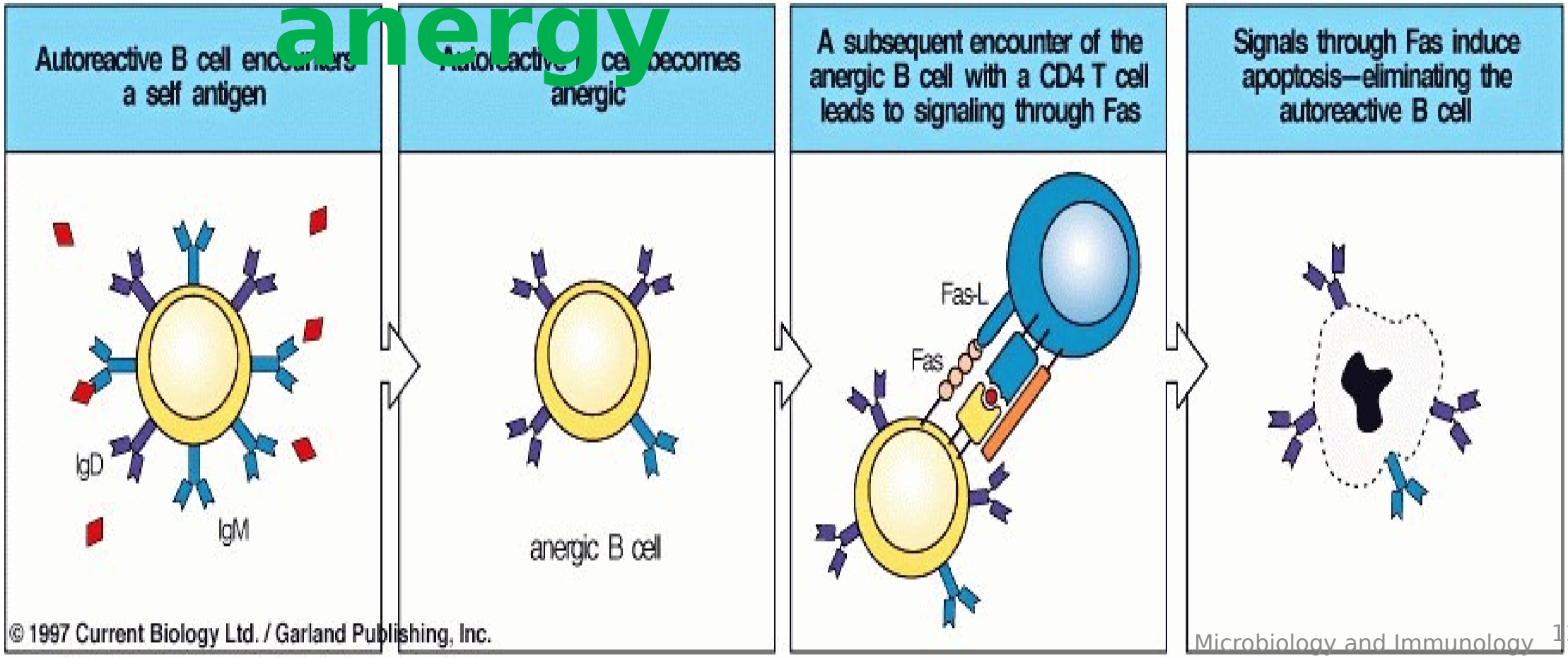


Tolerance


Antigen-presenting cell
Class II MHC
Antigen
TCR
Helper T cell
CD4 protein
B7 protein
CD28 protein
A
Antigen-presenting cell
Class II MHC
Antigen
TCR
Helper T cell
CD4 protein
CD28 protein
B

II- Peripheral Tolerance

Peripheral B-cell anergy



II- Peripheral Tolerance

B. Clonal Ignorance

Self-reactive T cells are kept ignorant due to one of two reasons :

Physical separation from the target antigens, (sequesterd Ags) e.g., the blood–brain barrier.

Self antigens are present in such small amounts.

II- Peripheral Tolerance

C. Deletion:

Repeated exposure of mature T lymphocytes by self antigen in peripheral tissues triggers apoptosis of self reactive T lymphocytes

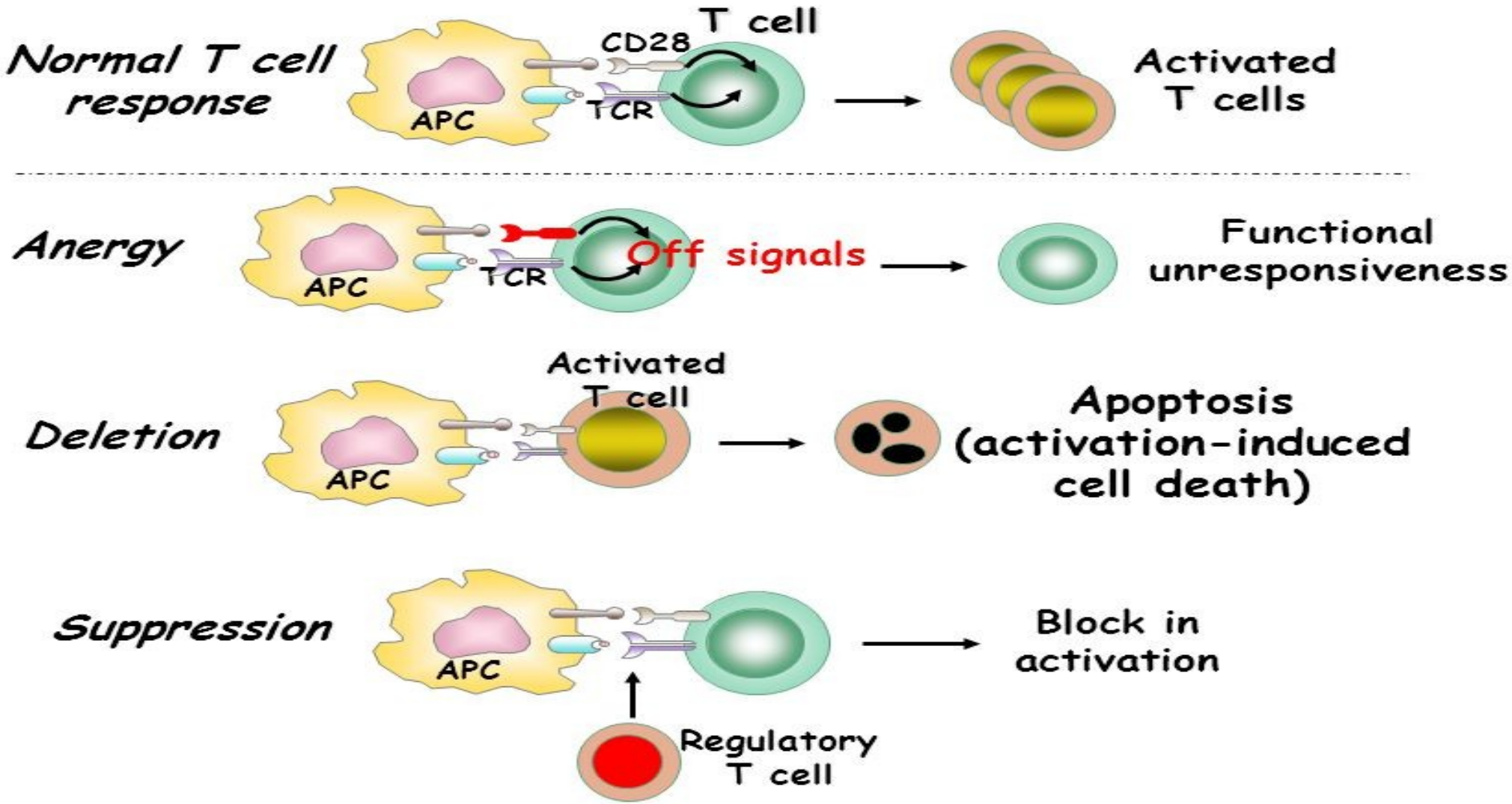
II- Peripheral Tolerance

D. Suppression by T reg cells:

Autoreactive T cells are prevented from reacting by Treg.

(regulatory T cells) that secrete IL10 & TGF-β

Peripheral tolerance



In a nut shell

- **Immune tolerance:**

Peripheral:

- ✓ **Clonal anergy**
- ✓ **Clonal ignorance**
- ✓ **Deletion**
- ✓ **Suppression by T regulatc**

Quiz

Which of the following represents a mechanism for central tolerance?

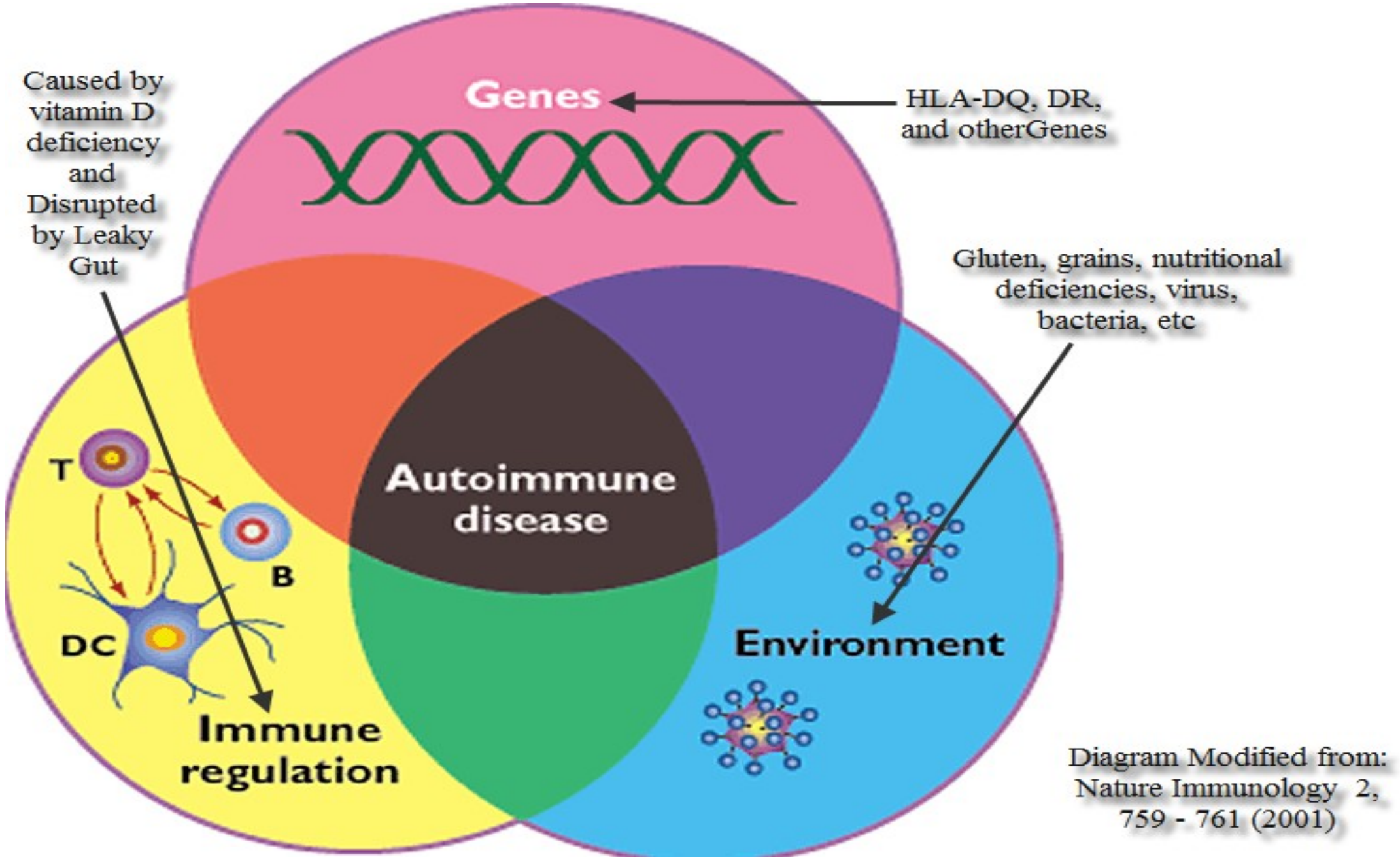
a. Clonal ignorance
b. Receptor editing
c. Clonal anergy
d. Apoptosis
e. Suppression by T regulatory cells

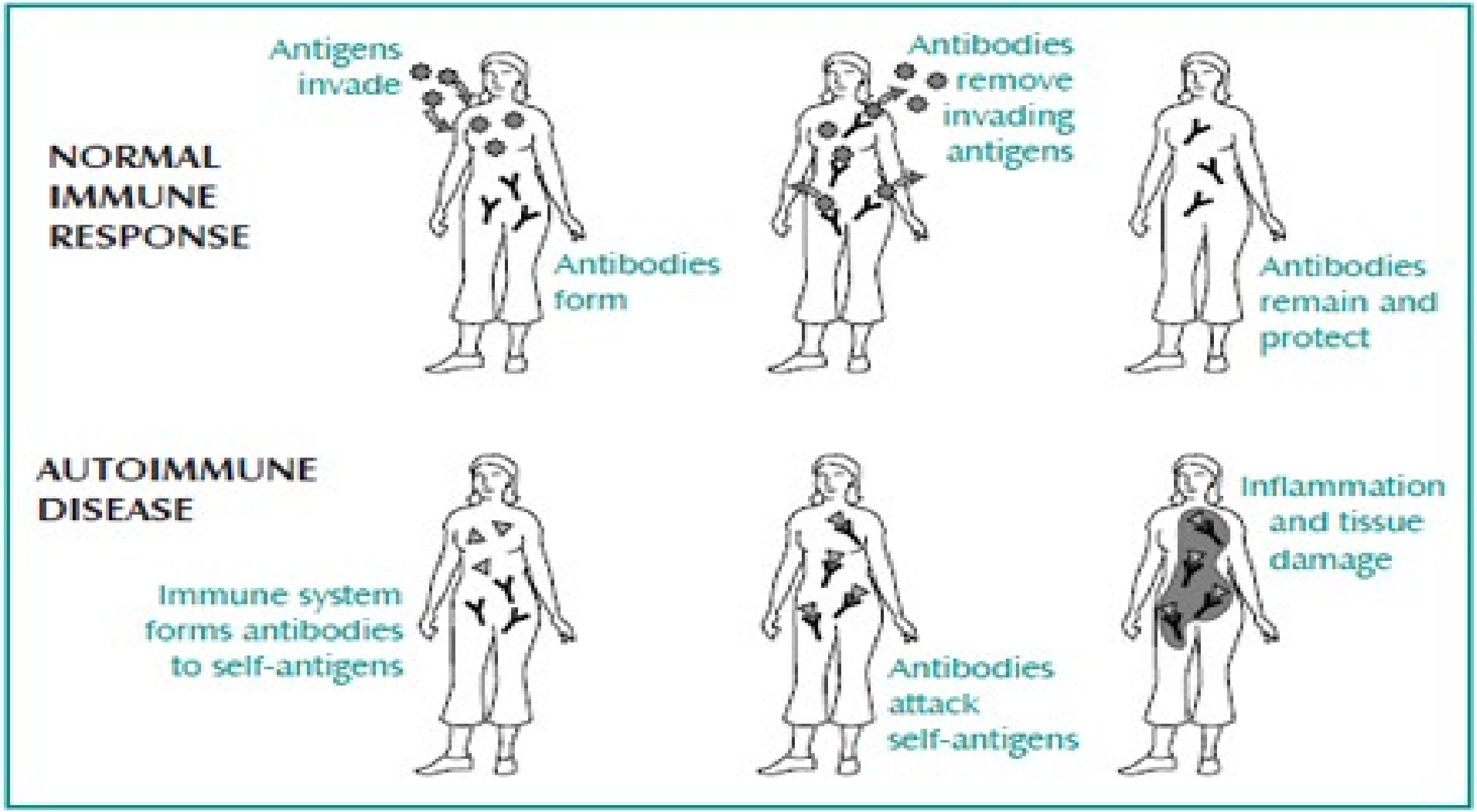

BREAK TIME

Autoimmune Diseases

* **Autoimmune diseases occur due to breakdown of the mechanisms that maintain auto tolerance**

* **Auto-antibodies and self reactive T-cells are produced, resulting in tissue damage by several mechanisms**


Caused by vitamin D deficiency and Disrupted by Leaky Gut
Genes
HLA-DQ, DR, and otherGenes
Gluten, grains, nutritional deficiencies, virus, bacteria, etc
T
B
DC
Autoimmune disease
Environment
Immune regulation
Diagram Modified from: Nature Immunology 2, 759 - 761 (2001)


NORMAL IMMUNE RESPONSE
Antigens invade
Antibodies form
Antibodies remove invading antigens
Antibodies remain and protect
AUTOIMMUNE DISEASE
Immune system forms antibodies to self-antigens
Antibodies attack self-antigens
Inflammation and tissue damage

Etiology of autoimmune diseases

I. Genetic

- **HLA association**

B27& ankylosing spondylitis	**DR4&rheumatoid arthritis**

- ***Abnormalities in genes*** encoding proteins that **regulate lymphocyte apoptosis**

Etiology of autoimmune disea

II. Sex:

↑ sex hormones in child bearing period

↑Autoimmune ds in ♀

as in Grave's ds, SLE, multiple sclerosis

Etiology of autoimmune disease

III. Environmental:

a. Infection & trauma:

- Microbial antigens which mimic or cross-react with self-components i.e Molecular mimicry
- Trauma: release of sequestered Ag
- Super antigens: as bacterial toxins

b. Alteration of self antigen: drugs, chemicals ...f.

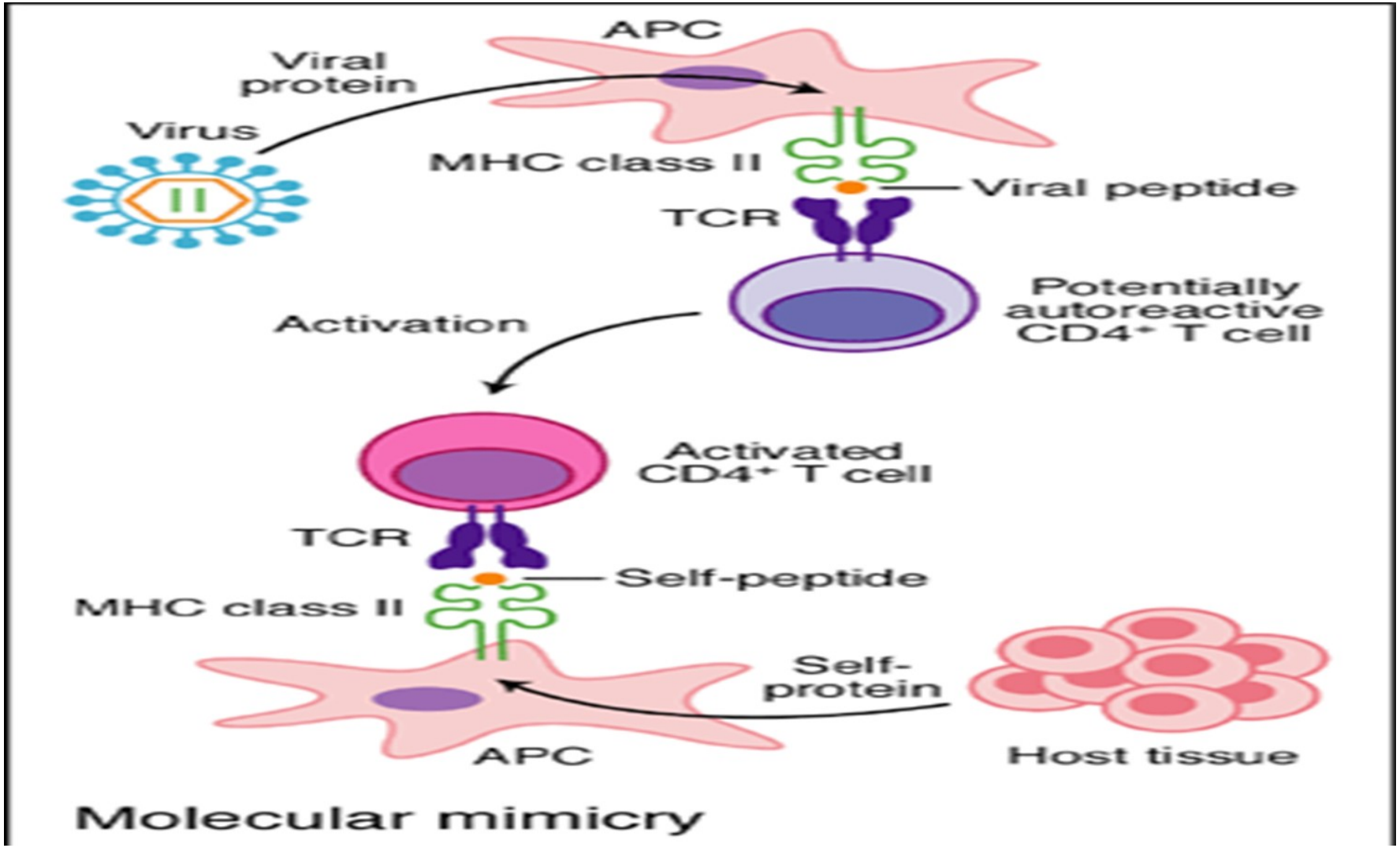
Drugs (haptens) coupling with RBCs alter self Ags

hemolytic anem...

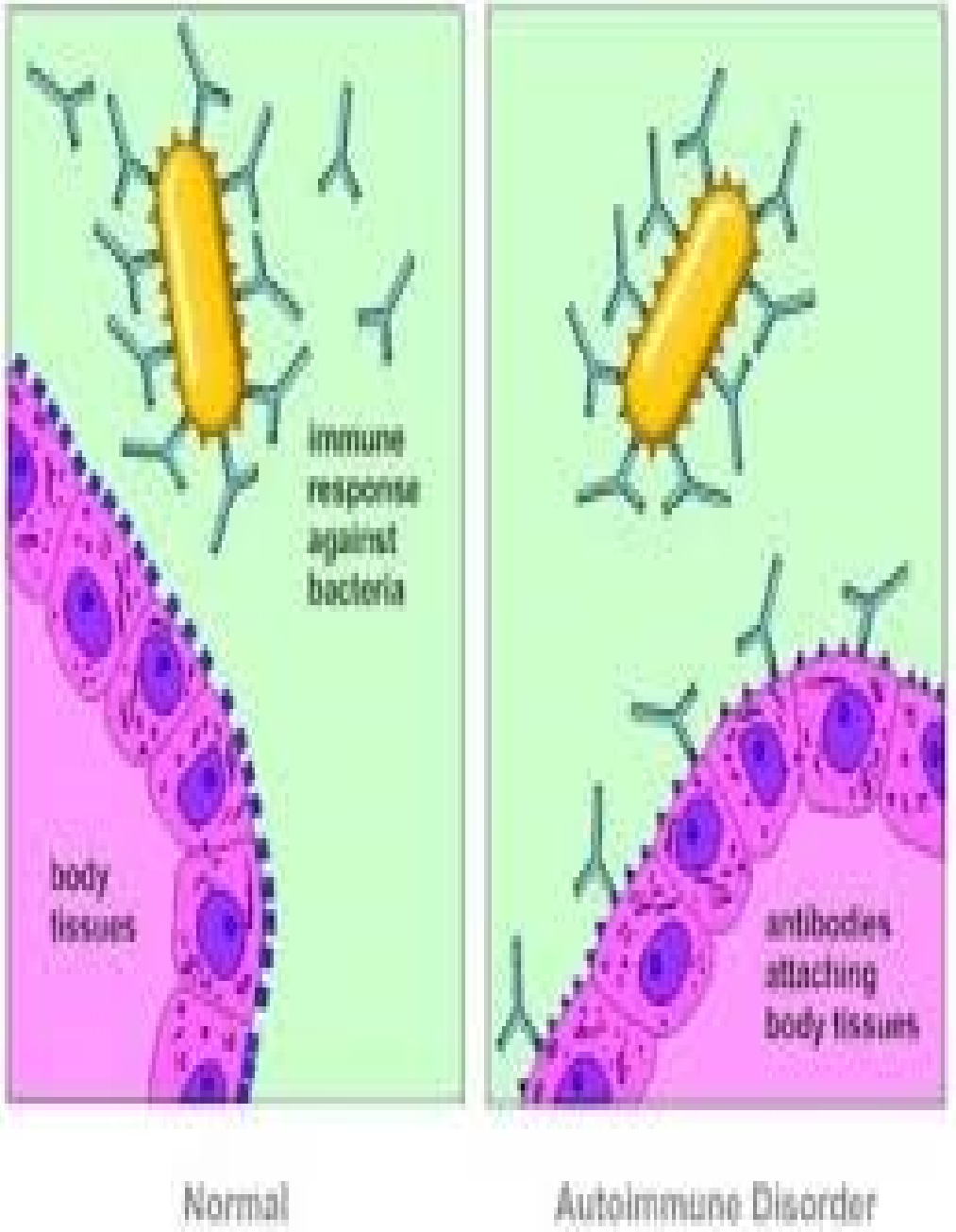
c. Loss of suppressi...

Decrease in no. of T reg with age Suppressed Self Reactive cells

Molecular mimicry



Microbe	Autoimmune Disease
Bacteria	
Streptococcus pyogenes	Rheumatic fever
Campylobacter jejuni	Guillain-Barré syndrome
Escherichia coli	Primary biliary cirrhosis
Yersinia enterocolitica	Reactive arthritis
Borrelia burgdorferi	Lyme arthritis
Viruses	
Hepatitis B virus[1]	Multiple sclerosis
Hepatitis C virus	Mixed cryoglobulinemia
Measles virus	Allergic encephalitis
Cytomegalovirus	Scleroderma
Human T-cell leukemia virus	HTLV-associated myelopathy



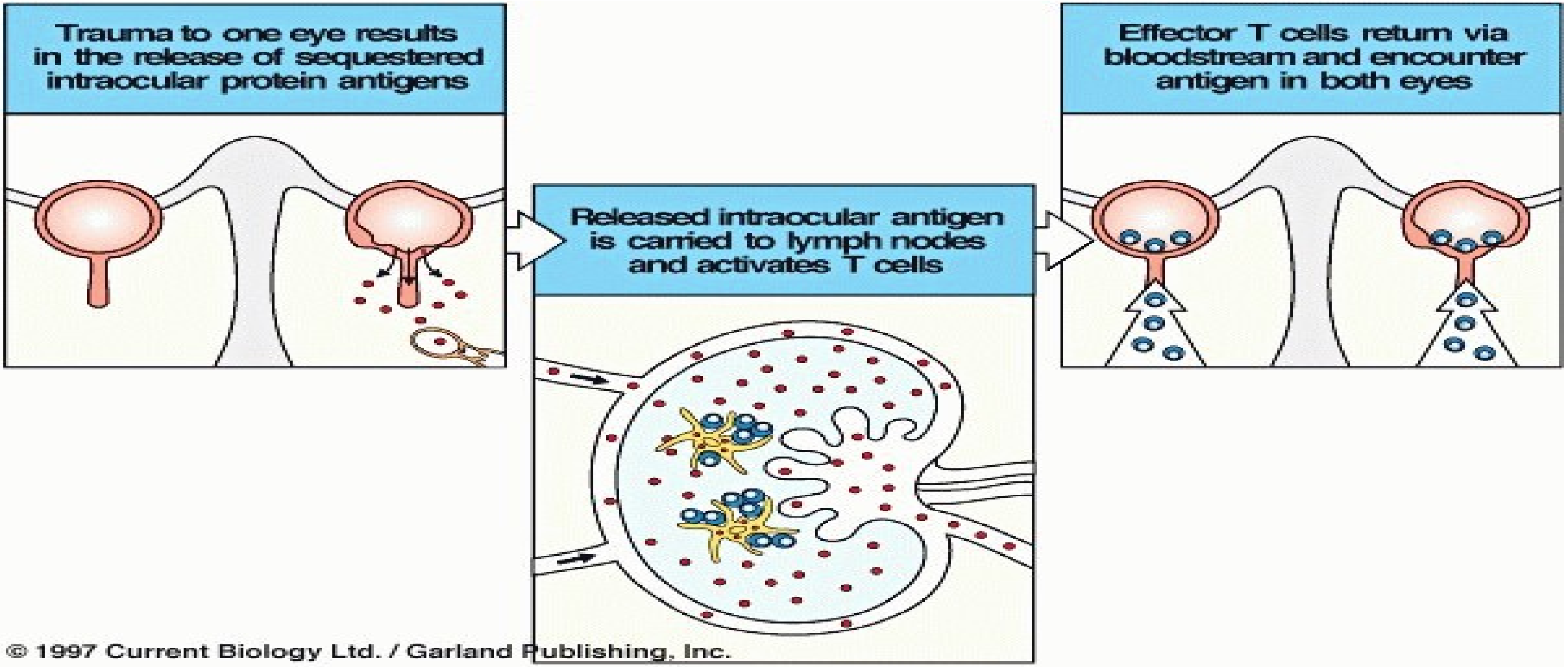
Trauma

Release of Sequestered Antigens

Certain tissues, e.g., sperm, central nervous system, and the lens and uveal tract of the eye, are sequestered so that their antigens are not exposed to the immune system.

These are known as immunologically privileged sites When such antigens enter the circulation accidentally, e.g., after damage, they elicit both humoral and cellular responses, producing aspermatogenesis, encephalitis, or endophthalmitis, respectively.

Damage to an immunologically privileged site can induce an autoimmune response



Quiz

All of the following probably contribute to the development of autoimmunity EXCEPT

a. cross-reactivity of pathogen and self antigens.

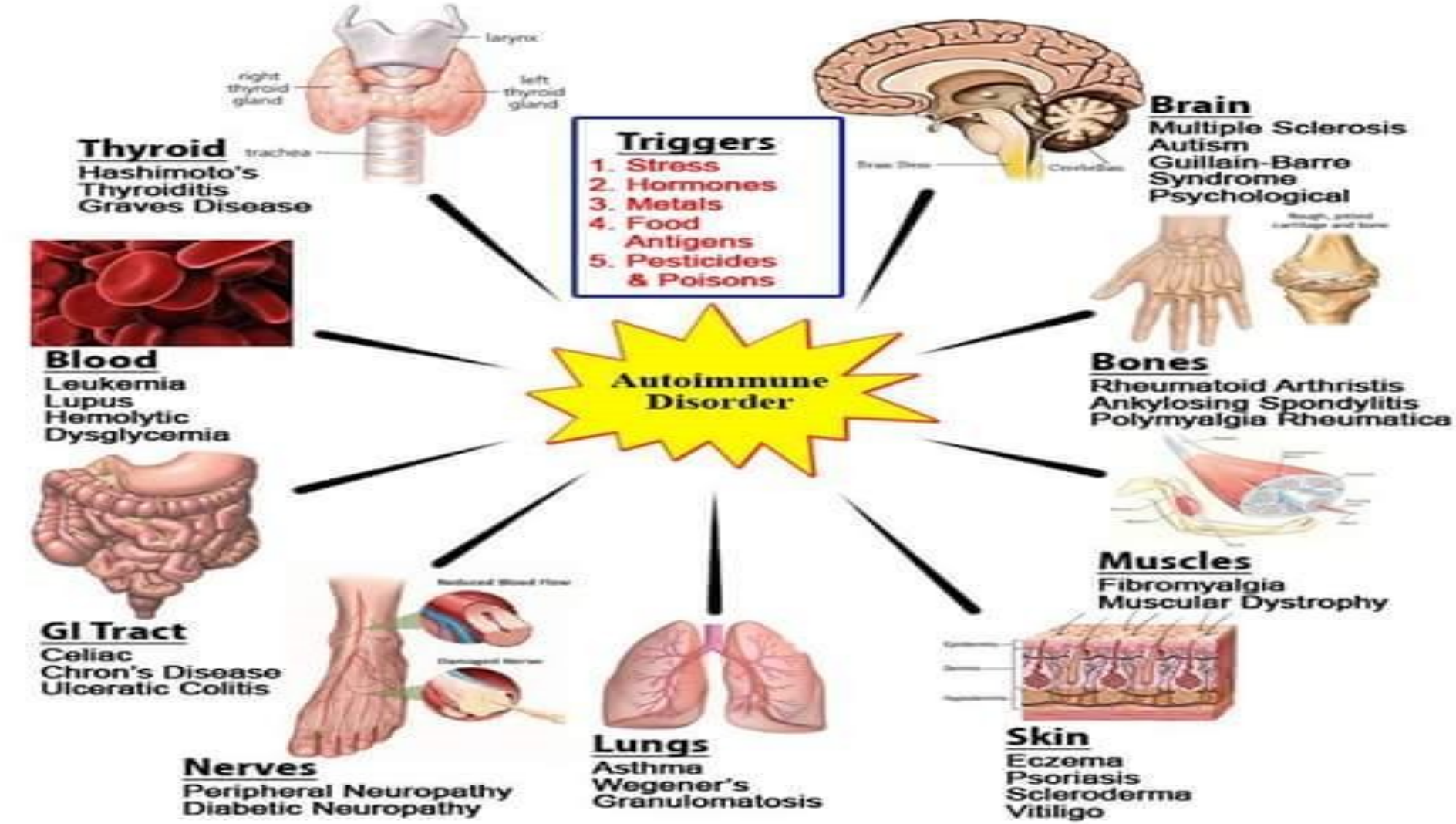
b. expression of self antigen in the thymus or bone marrow.

c. low avidity presentation of some self peptides in the thymus.

d. random generation of TCR and BCR specificities.

e. tissue injury which releases normally hidden self antigens.

Tissues of The Body Affected By Autoimmune Attack

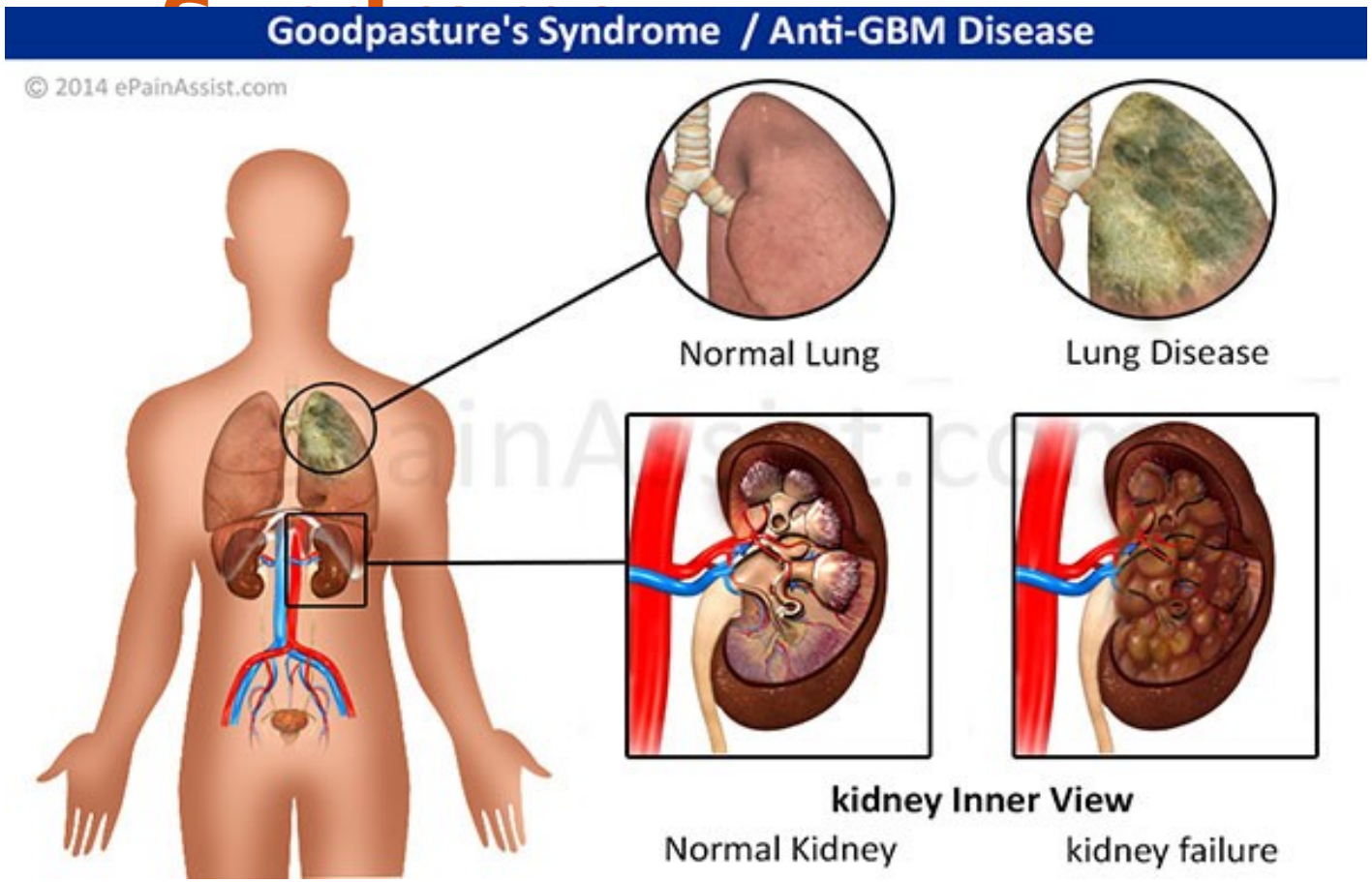


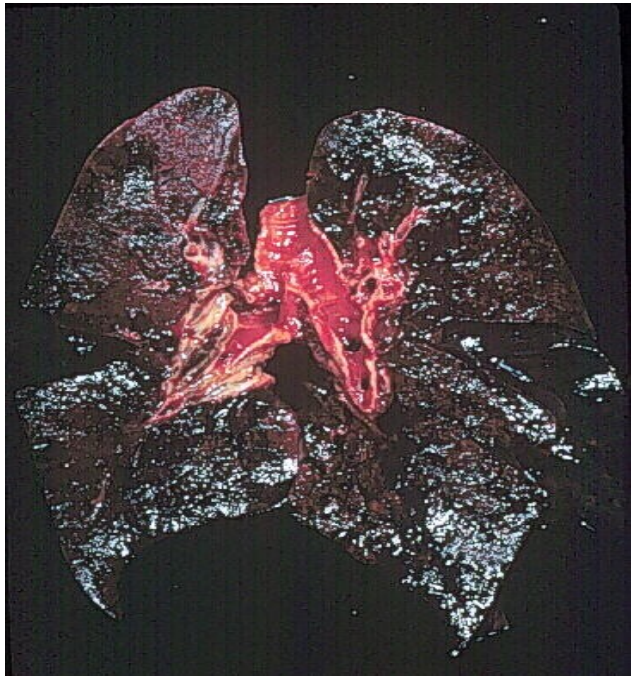
Autoimmune diseases mediated by cytotoxic antibodies (Type II)

Syndrome	Autoantigen	Consequences
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes, anemia
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction

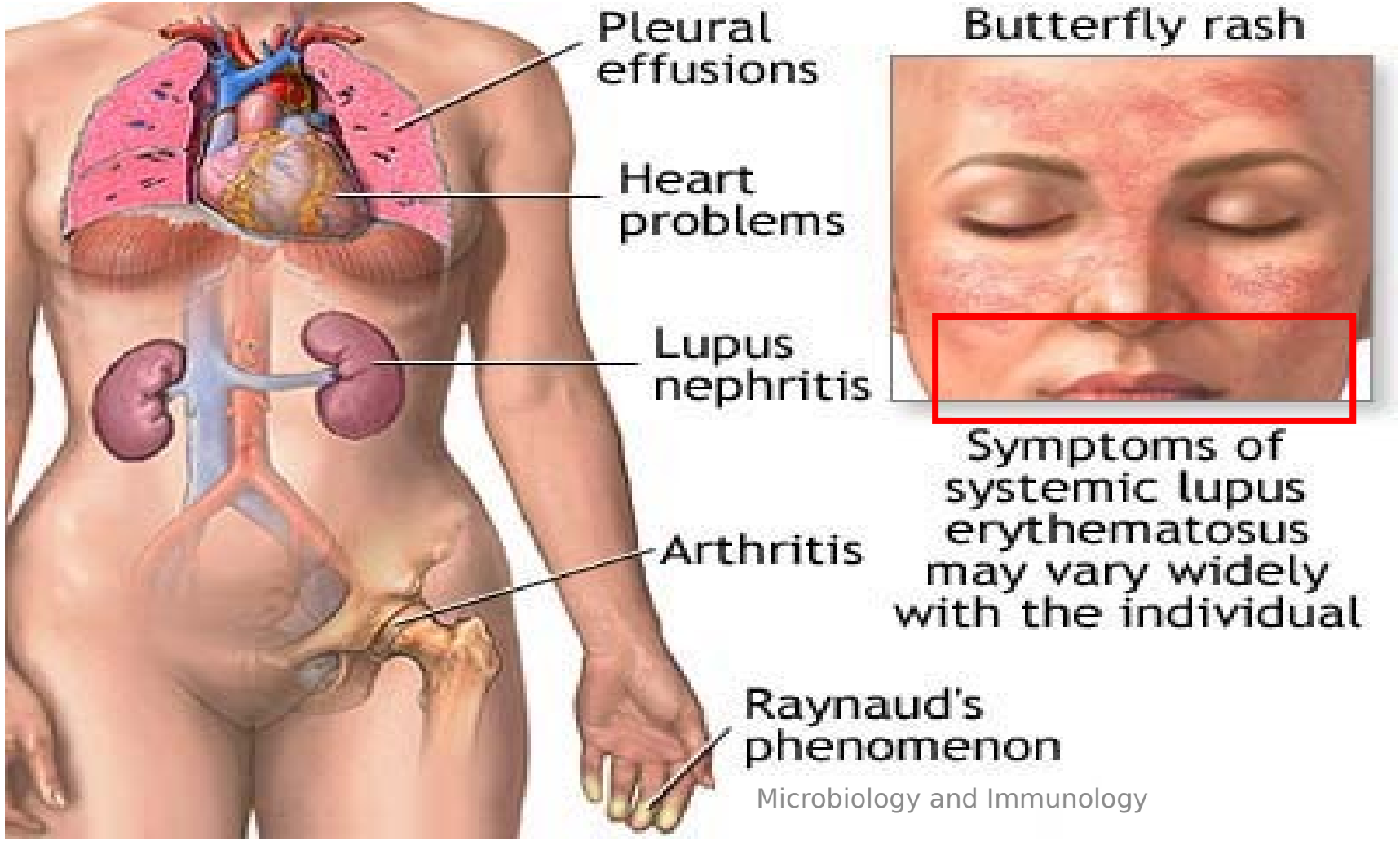
Diseases Involving Multiple Organs (Systemic Diseases):

Goodpasture's Syndrome





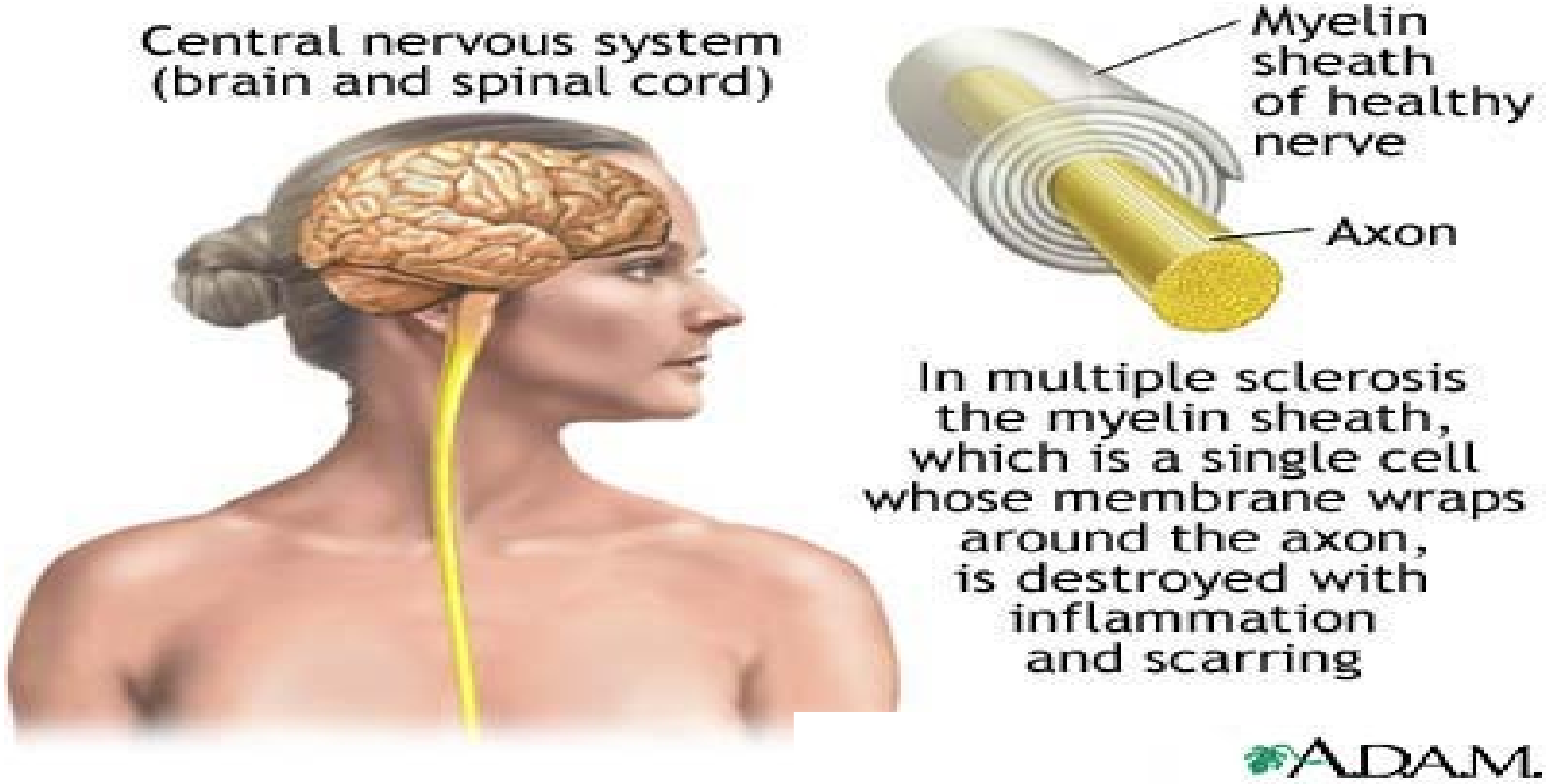
Examples of Systemic Autoimmun



Symptoms of systemic lupus erythematosus may vary widely with the individual

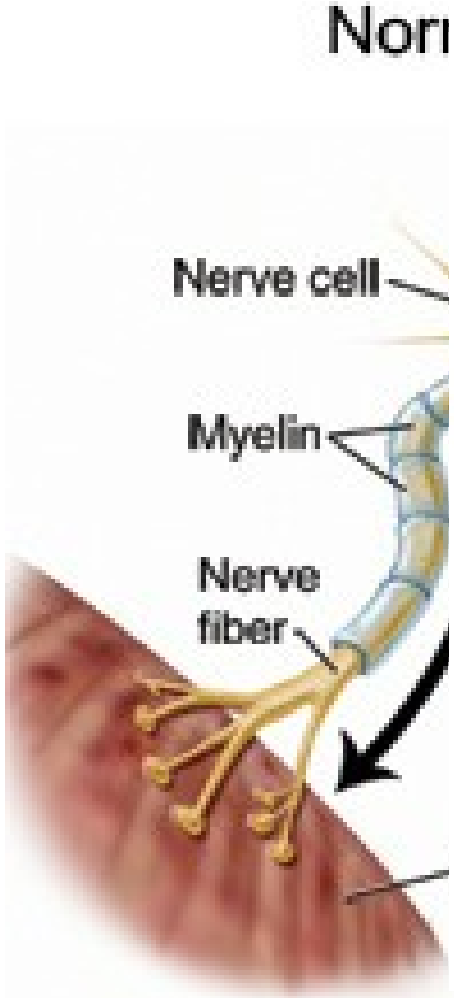
SLE

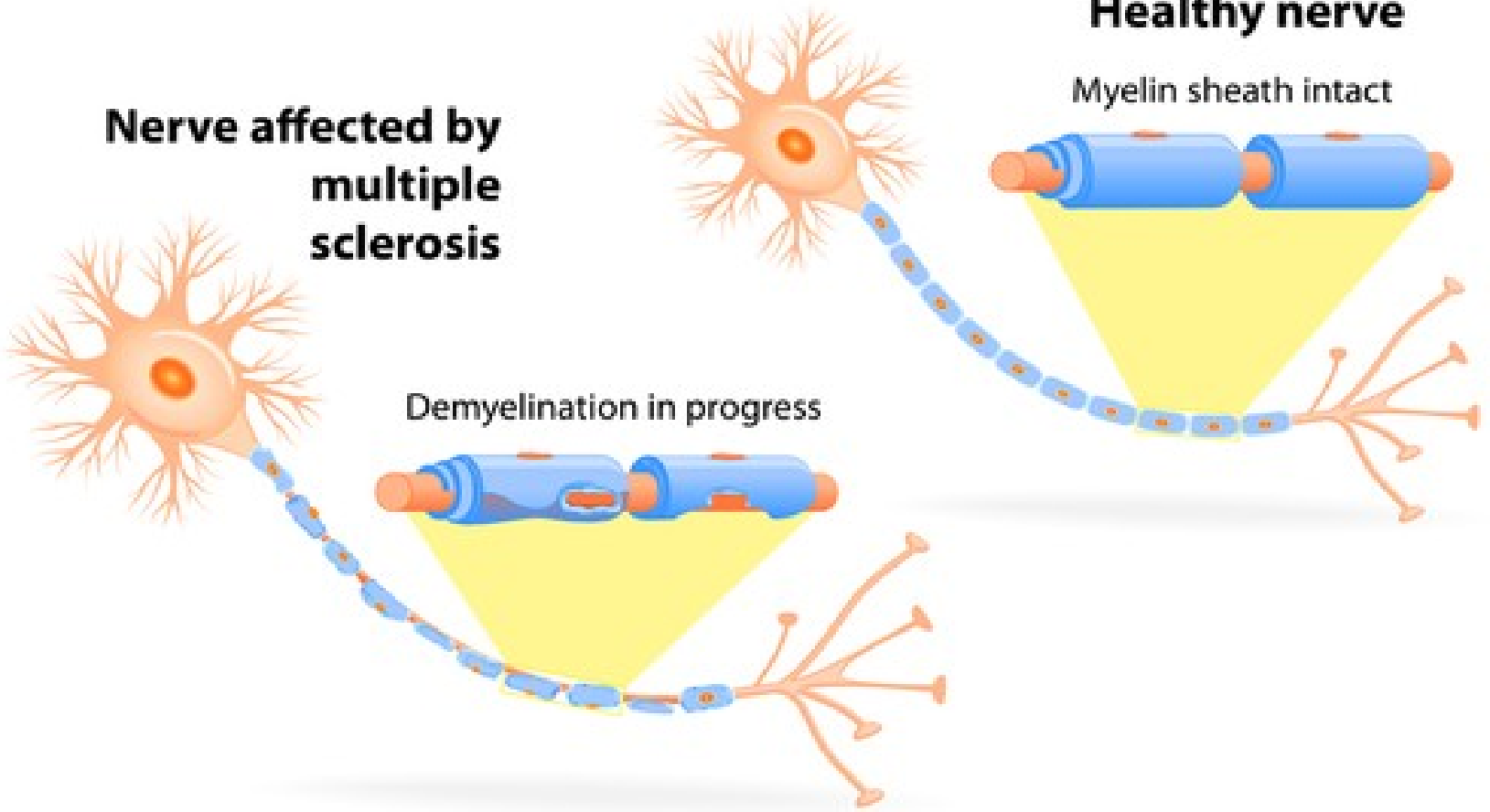
Multiple Sclerosis/ Guillain Barre Syndrome



MS patients can have autoantibodies and/or self reactive T cells which are responsible for the demyelination

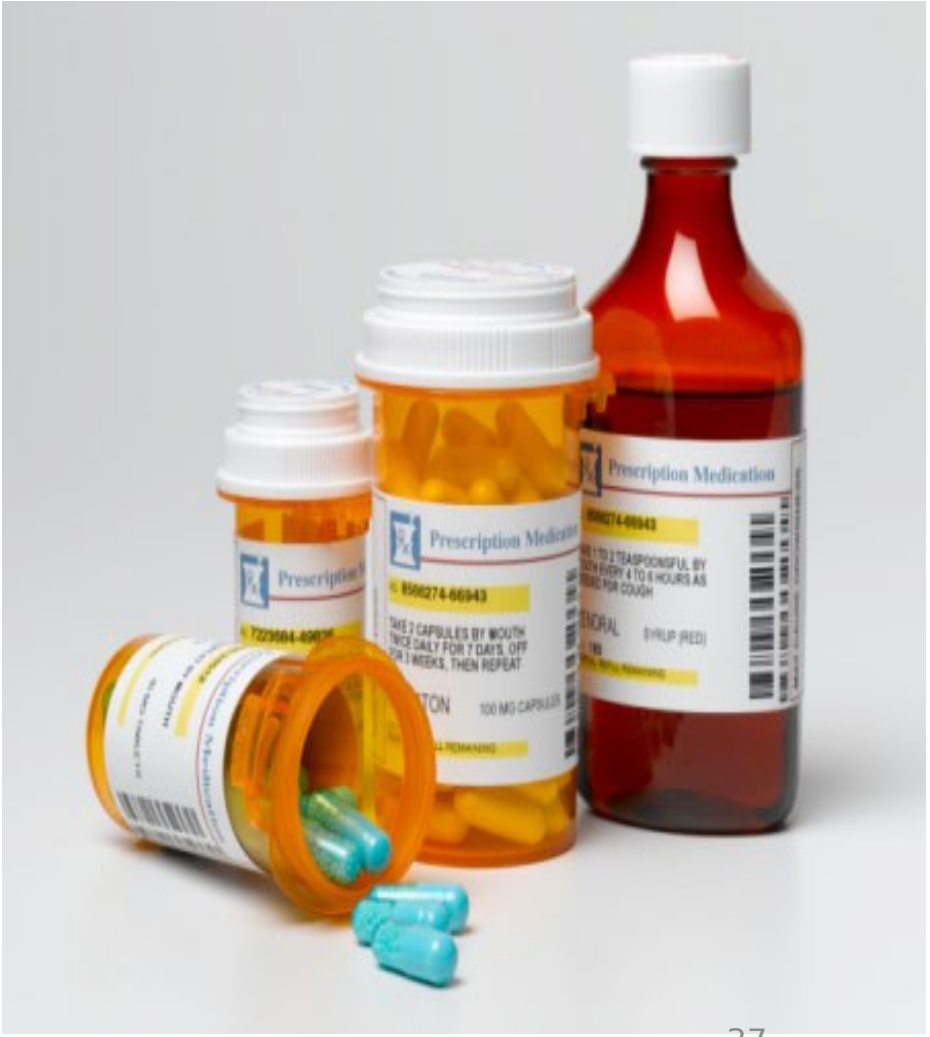
Multiple Sclerosis/ Guillain Barre Syndrome





Treatment Strategies

The key to treat autoimmunity is immunomodulation



A. Drug therapy

- Cytotoxic drugs,
- Anti-inflammatory drugs as cortisone or NSAID
- Immunosuppressive drugs.

B-Old trials include:

- Plasmapharesis to remove autoimmune antibodies or complexes.
- Antilymphocyte sera to deplete T lymphocyte.

B. Recently several trials include

Selective immunotherapy for autoimmune diseases:

now seems attainable, with the many possible "points of engagement"

1-Monoclonal antibodies as anti CD3, anti TCR and anti B cell Ig receptor to block T and B lymphocyte stimulation.

2-Inhibition of Th1 cytokines or inflammatory cytokines by Monoclonal antibodies as anti IL-2, anti TNF-a

3-T regulatory cells administration: They suppress lymphocyte stimulation by self-antigens either by direct contact or by secretion of inhibitory cytokines.

Quiz

Which of the following denotes genetic factor as an etiology of autoimmune diseases?

a) Defective apoptosis

b) Clonal deletion

c) Epitope spreading

d) Increased sex hormones

e) Altered self antigens

Quiz

Monoclonal antibodies used in treatment of autoimmune diseases are directed against which of the following?

a. CD4

b. CD8

c. CD28

d. CD40

e. CD3

SUGGESTED TEXTBOOKS

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1. ***Review of Medical Microbiology and Immunology, Warren Levinson Chapter 66 p. 1214: 1231***
2. ***Cellular and molecular Immunolgy , Abul Abbas & Lichtmann Chapter 15 p.315:335***


THANK
YOU